Proposed Registration Decision PRD2016-14

Amitraz

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Overview

Proposed Registration Decision for Amitraz

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing a renewal of the conditional registration for the sale and use of Amitraz Technical and Apivar Strips, containing the technical grade active ingredient amitraz, to control the parasitic mite (*Varroa destructor*) on honeybees.

Amitraz Technical (Registration Number 23485) is fully registered in Canada for use in tick collars for dogs. The same technical is used in the manufacture of Apivar Strips (Registration Number 29092) which was granted conditional registration in Canada in 2012. The detailed review for Amitraz Technical and the Apivar Strips product can be found in ERC2013-04, *Amitraz*. Apivar Strips are used in honeybee hives for the purpose of controlling Varroa mite (*Varroa destructor*), which is a parasitic mite that can infest beehives, impacting bee health and reduce bee populations in the hive.

The original evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment. Although the risks and value have been found to be acceptable when all risk reduction measures are followed, as a condition of the original registrations, additional scientific information was requested from the applicant in order to confirm the scientific assumptions that formed part of the risk assessment for the Apivar Strips product. In support of the request to renew the conditional registrations, a rationale for renewal of the registrations was provided.

The requirement to submit additional scientific information as a condition of registration remains.

This Overview describes the key points of the original evaluation, while the Science Evaluation in ERC2013-04, *Amitraz* provides detailed technical information on the human health, environmental and value assessments of Amitraz Technical and Apivar Strips.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "... the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which

to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of the Health Canada website.

Before making a decision to renew the conditional registrations of Amitraz Technical, for use in the manufacture of Apivar Strips, and the Apivar Strips product, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on the use of Amitraz Technical and Apivar Strips, which will include the decision, the reasons for it, a summary of comments received on the proposed renewal of the conditional registration and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation in ERC2013-04, *Amitraz*.

What Is Amitraz?

Amitraz is a pesticide that is used for the control of insects, and in this instance specifically for the control of Varroa mites. It appears to act on the nervous system, leading to overexcitation and consequently paralysis and death in arthropod pests.

Apivar Strips consist of a plastic polymer strip embedded with amitraz. The strips are placed in the hive with one strip used for every five frames of bees in each brood chamber. The strip is hung between the frames, with the frames separated slightly so that both sides of the strip come into contact with the bees. The bees rub against the strips as they move through the brood chamber, and then pass the chemical on to other bees as they rub up against each other in the hive. The strips should be removed after six weeks.

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it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Health Considerations

Can Approved Uses of Amitraz Affect Human Health?

Amitraz is unlikely to affect your health when used according to label directions.

Potential exposure to amitraz may occur through the diet (food only) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100 times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, the acute oral toxicity of the technical grade active ingredient amitraz varies widely among species. Amitraz was of low toxicity in mice and of high toxicity in several other test species via the oral route. Amitraz was slightly toxic via the dermal route, of low toxicity via the inhalation route, minimally irritating to the eyes and skin, and was determined to be a potential skin sensitizer.

The acute toxicity data for the active ingredient were used to characterize the hazard of the end-use product, Apivar Strips. Although data indicated that amitraz may be highly acutely toxic via the oral route, this route was not expected to be of concern with the proposed use since the active ingredient is embedded in plastic strips. Overall, Apivar Strips were considered to be slightly acutely toxic via the dermal route, of low acute toxicity via the inhalation route, minimally irritating to the eyes and skin, and capable of causing allergic skin reactions. Consequently the signal words "CAUTION POISON" and "POTENTIAL SKIN SENSITIZER" are required on the product label.

Registrant-supplied short, and long term (lifetime) animal toxicity tests, as well as information from the published scientific literature were assessed for the potential of amitraz to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The available toxicology studies indicate the main effects caused by amitraz were related to suppression of the central nervous system, and included sedation, as well as decreases in body temperature, blood pressure and heart rate. Generally, these effects tended to have a rapid onset, were short-lived, and did not appear to accumulate over time. Amitraz did not damage genetic material and was not considered to pose a cancer risk. When amitraz was given to pregnant rats, effects on the urinary system of the developing fetus were observed at doses that also caused effects in the maternal animals, indicating that the young do not appear to be more sensitive to amitraz than the adult animal. However, it was not possible to fully describe the effects on young and developing animals, as the full complement of studies

required to fully assess these effects was not available. To address this, an extended one-generation reproductive toxicity study, including a developmental neurotoxicity component, is currently being conducted for submission to the Agency. In lieu of this study, an additional protective factor was used in the risk assessment to further reduce the allowable level of human exposure to amitraz (refer to ERC2013-04, *Amitraz*, page 4). Furthermore, consideration was given to the anticipated low exposure potential resulting from the physical form of the product as well as the dietary and occupational exposure aspects outlined below.

Residues in Water and Food

Dietary intake estimates (food only) revealed that the general population is expected to be exposed to less than 4.3% of the acceptable daily intake. A dietary intake estimate (food only) for the highest exposed population (children 1-2 years old) used less than 25.42% of the acute reference dose, which is not a health concern. Based on these estimates, the chronic and acute dietary risks from amitraz are not of concern for all population sub-groups.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Supervised residue trials conducted in France according to the Canadian use pattern were found acceptable to support the registration of Apivar Strips in Canada. The MRL for this active ingredient can be found in the Science Evaluation of ERC2013-04, *Amitraz*.

Risks in Residential and Other Non-Occupational Environments

Due to the nature of the application and the treatment location, bystander and residential exposures are not of concern.

Occupational Risks From Handling Apivar Strips

Apivar Strips are sustained-release, hardened plastic strips containing amitraz. For workers handling the strips, exposure via the inhalation route is expected to be minimal, and relative to the dermal exposure incurred, it is expected to be negligible.

The use of amitraz in honeybee colonies potentially represents a risk of concern for users handling the Apivar Strips; however, the mitigation measures recommended on the label, such as the use of chemical-resistant gloves (for example, nitrile), should address this risk. In conducting the risk assessment for the use of Apivar Strips, the PMRA made certain assumptions based on the toxicology studies on file for amitraz and the anticipated user exposure when handling the Apivar Strips. The risk assessment has incorporated added measures of protection to further reduce potential exposure and the outstanding scientific information is expected to confirm the assumptions that have been made. This information is expected to be sent to the Agency by August 2016.

No restricted entry interval is required on the end-use product label for Apivar Strips.

Environmental Considerations

What Happens When Amitraz Is Introduced Into the Environment?

Based on the use pattern, amitraz is unlikely to be introduced into the environment, and therefore the risk to non-target organisms is considered to be negligible, when used according to the label directions.

Value Considerations

What Is the Value of Apivar Strips?

Apivar Strips have value as they control varroa mites (*Varroa destructor*) in honeybee hives.

Varroa mites are the most important parasitic pest of honeybees, and have a severe economic impact on the Canadian beekeeping industry. Significant varroa mite infestations in a honeybee colony will cause the loss of the infested colonies. Varroa mites are the main cause of honeybee colony loss in Canada.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being placed on the label of Apivar Strips to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Since there is a potential for users to come into direct contact with amitraz on the skin, anyone applying Apivar Strips must wear chemical-resistant gloves (for example, nitrile). In addition, the label statement "Do not handle more than 100 pairs of strips per person per day." is required on the label.

Environment

Standard precautionary measures are required to mitigate potential risks to non-target organisms. These include adding precautionary statements to the label regarding environmental hazards and the directions for use.

What Additional Scientific Information Is Being Requested?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the applicant must submit additional scientific information as a condition of registration. More details are presented in the Science Evaluation of ERC2013-04, *Amitraz* or in the Section 12 Notice associated with these conditional registrations. The applicant must submit the following information by 1 September 2016.

Human Health

The following data, which have also been identified as part of the ongoing PMRA re-evaluation, will have to be addressed as a condition of registration of the technical active ingredient used in the Apivar Strips:

- DACO 4.5.3 – Prenatal developmental toxicity study in rabbits
- DACO 4.5.1 – Rat reproductive toxicity study
- DACO 4.5.14 – Developmental neurotoxicity study
- DACO 4.5.12 – Acute neurotoxicity*
- DACO 4.5.13 – 90-day neurotoxicity*

*As mentioned in ERC2013-04, these studies have already been submitted to the Agency. In addition, significant progress has been made towards satisfying the requirement for the remaining scientific information outlined above. Specifically, the PMRA has provided detailed comments on a new protocol for an extended one-generation reproductive toxicity study, which includes a developmental neurotoxicity component.

Next Steps

Before making a decision to renew the conditional registration of Amitraz Technical, for use in the manufacture of Apivar Strips, and Apivar Strips to control the parasitic mite (*Varroa destructor*) on honeybees, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include the decision, the reasons for it, a summary of comments received on the proposed renewal of the conditional registrations and the PMRA's response to these comments.

Other Information

When the PMRA makes its decision on the renewal of the conditional registration of the use of Amitraz Technical and Apivar Strips, it will publish a Registration Decision on amitraz (based on the Science Evaluation in ERC2013-04). In addition, the test data referenced in ERC2013-04 will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).